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Oocket No. INN-123
Patent Application

In the Claims

Claims 1-79 (Canceled).

Claim 80 (New): A method of treating a disease comprising the administration of a composition $\gamma\delta$ cell activator comprising a pharmaceutically acceptable carrier in an amount sufficient to induce an at least 5-fold increase in the $\gamma\delta$ T cell population in a subject, wherein said disease is selected from the group consisting of cancer, solid tumors, infectious diseases, autoimmune diseases and allergic disease.

Claim 81 (New): The method according to claim 80, wherein said $\gamma\delta$ T cell activator is provided in an amount sufficient to induce an at least 10-fold increase in the $\gamma\delta$ T cell population in a subject.

Claim 82 (New): The method according to claim 80, wherein at least two treatments are administered to said subject.

Claim 83 (New): The method according to claim 80, wherein at least four treatments are administered to said subject.

Claim 84 (New): The method according to claim 80, wherein the $\gamma\delta$ T cell activator is administered in more than one treatment with an interval of about two to about eight weeks between treatments.

Claim 85 (New): The method according to claim 80, wherein the $\gamma\delta$ T cell activator is administered in more than one treatment with an interval of about three to about four weeks between treatments.

Claim 86 (New): The method according to claim 80, wherein said $\gamma\delta$ T cell activator is provided in an amount sufficient to expand the $\gamma\delta$ T cell population in a subject to reach between 30-90% of total circulating lymphocytes in a subject.

Claim 87 (New): The method according to claim 80, wherein the biological activity of $\gamma\delta$ T cells are increased in said subject.

Claim 88 (New): The method according to claim 80, wherein the solid tumor is renal cancer.

Claim 89 (New): The method according to claim 80, wherein said solid tumor is selected from the group consisting of a melanoma, ovarian cancer, colon cancer, lung cancer, pancreatic cancer, neuroblastoma, head or neck cancer, bladder cancer, breast cancer, brain cancer and gastric cancer.

Claim 90 (New): The method according to claim 80, wherein the $\gamma\delta$ T cell activator is a composition comprising a compound capable of inducing the proliferation of a $\gamma\delta$ T cell in a pure population of $\gamma\delta$ T cell clones when said compound is present in culture at a concentration of less than 1 mM.

Claim 91 (New): The method according to claim 80, wherein the $\gamma\delta$ T cell activator is a compound of formula (I):

$$R - A = \begin{cases} O & D \\ O \cdot Cat^{+} \end{cases} \qquad O \cdot Cat^{+}$$

Formula (I)

wherein Cat+ represents at least one organic or mineral cation that can be the same or different; m is an integer from 1 to 3;

B is O, NH, or any group capable of being hydrolyzed;

Y = O'Cat+; a C₁-C₃ alkyl group; -A-R; or a radical selected from the group consisting of a nucleoside, an oligonucleotide, a nucleic acid, an amino acid, a peptide, a protein, a monosaccharide, an oligosaccharide, a polysaccharide, a fatty acid, a simple lipid, a complex lipid, a folic acid, a tetrahydrofolic acid, a phosphoric acid, an inositol, a vitamin, a co-enzyme, a flavonoid, an aldehyde, an epoxyde and a halohydrin;

A is O, NH, CHF, CF₂ or CH₂; and,

R is a linear, branched, or cyclic, aromatic, non-aromatic, saturated or unsaturated C₁-C₅₀ hydrocarbon group, optionally interrupted by at least one heteroatom, wherein said hydrocarbon group comprises an alkyl, an alkylenyl, an alkynyl or an alkylene, which can be substituted by one or several substituents selected from the group consisting of: an alkyl, an alkylenyl, an alkynyl, an epoxyalkyl, an aryl, an heterocycle, an alkoxy, an acyl, an alcohol, a carboxylic group (-COOH), an ester, an amine, an amino group (-NH₂), an amide (-CONH₂), an imine, a nitrile, an hydroxyl (-OH), a aldehyde group (-CHO), a halogen, a halogenoalkyl, a thiol (-SH), a thioalkyl, a sulfone, a sulfoxide, and a combination thereof.

Claim 92 (New): The method according to claim 91, wherein the $\gamma\delta$ T cell activator is a compound of formula (II):

$$X \longrightarrow C \longrightarrow (CH_2)n \longrightarrow A \longrightarrow P \longrightarrow B \longrightarrow m P \longrightarrow Y$$

$$\downarrow P \longrightarrow B \longrightarrow m P \longrightarrow Y$$

$$\downarrow O-Cat+ O-Cat+ (II)$$

in which X is an halogen, B is O or NH, m is an integer from 1 to 3, R1 is a methyl or ethyl group, Cat+ represents at least one organic or mineral cation, n is an integer from 2 to 20, A is O, NH, CHF, CF₂ or CH₂, and Y is O Cat+, a nucleoside, or a radical –A-R, wherein R is selected from the group consisting of:

1)

$$-- (CH_2)_n -- C -- R_2$$
 R_1

wherein n is an integer from 2 to 20, R_1 is a (C_1-C_3) alkyl group, and R_2 is an halogenated (C_1-C_3) alkyl, a (C_1-C_3) alkoxy- (C_1-C_3) alkyl, an halogenated (C_2-C_3) acyl or a (C_1-C_3) alkoxy- (C_2-C_3) acyl;

2)

$$-(CH_2)_n R_1$$

wherein n is an integer from 2 to 20, and R_1 is a methyl or ethyl group; and 3)

$$- \begin{matrix} \begin{matrix} R_3 \\ \\ \\ C \end{matrix} - W = C \end{matrix} = \begin{matrix} \begin{matrix} R_5 \\ \\ R_6 \end{matrix}$$

wherein R_3 , R_4 , and R_5 are identical or different and are a hydrogen or (C_1-C_3) alkyl group, W is – CH- or –N- and R_6 is an (C_2-C_3) acyl, an aldehyde, an (C_1-C_3) alcohol, or an (C_2-C_3) ester.

Claim 93 (New): The method according to claim 92, wherein the compound of formula (II) is (R, S)-3-(bromomethyl)-3-butanol-1-yl-diphosphate.

Claim 94 (New): The method according to claim 92, wherein the $\gamma\delta$ T cell activator is administered in a dose to humans between 10 mg/kg to 100 mg/kg.

Claim 95 (New): The method according to claim 92, wherein said $\gamma\delta$ T activator is administered by intravenous infusion in a dose to humans that is calculated according to the formula (I): single dose (mg/kg)=(10 to 100) * N (I), where N is the number of weeks between treatments such that N is between about 3 and about 4.

Claim 96 (New): The method according to claim 91, wherein the γδ T cell activator is a compound of formula (XII):

R5
$$C = W - C - A - P - B - P - Y$$
R6 $C = W - C - A - P - B - P - Y$
R6 $C = W - C - A - P - B - P - Y$
R6 $C = W - C - A - P - B - P - Y$
R6 $C = W - C - A - P - B - P - Y$
R6 $C = W - C - A - P - B - P - Y$
R6 $C = W - C - A - P - B - P - Y$
R6 $C = W - C - A - P - B - P - Y$
R7 $C = W - C - A - P - B - P - Y$
R8 $C = W - C - A - P - B - P - Y$

in which R_3 , R_4 , and R_5 are identical or different and are a hydrogen or (C_1-C_3) alkyl group, W is – CH- or –N-, R_6 is an (C_2-C_3) acyl, an aldehyde, an (C_1-C_3) alcohol, or an (C_2-C_3) ester, Cat+ represents at least one organic or mineral cation that can be the same or different, B is O or NH, m is an integer from 1 to 3, A is O, NH, CHF, CF₂ or CH₂, and Y is O Cat+, a nucleoside, or a radical –A-R, wherein R is selected from the group consisting of:

1)

$$-- (CH_2)_n -- C -- R_2$$
 R_1

wherein n is an integer from 2 to 20, R_1 is a (C_1-C_3) alkyl group, and R_2 is an halogenated (C_1-C_3) alkyl, a (C_1-C_3) alkoxy- (C_1-C_3) alkyl, an halogenated (C_2-C_3) acyl or a (C_1-C_3) alkoxy- (C_2-C_3) acyl; 2)

$$- (CH2)n R1$$

wherein n is an integer from 2 to 20, and R₁ is a methyl or ethyl group; and

3)

$$- \overset{R_3}{\underset{R_4}{\overset{}{\bigcirc}}} - w = \overset{R_5}{\underset{R_6}{\overset{}{\bigcirc}}}$$

wherein R_3 , R_4 , and R_5 are identical or different and are a hydrogen or (C_1-C_3) alkyl group, W is CH or N, and R_6 is an (C_2-C_3) acyl, an aldehyde, an (C_1-C_3) alcohol, or an (C_2-C_3) ester.

Claim 97 (New): The method according to claim 96, wherein the compound of formula (XII) is (E)-4-hydroxy-3-methyl-2-butenyl pyrophosphate.

Claim 98 (New): The method according to claim 96, wherein the compound of formula (XII) is (E)-5-hydroxy-4-methylpent-3-enyl pyrophosphonate.

Claim 99 (New): The method according to claim 96 where said $\gamma\delta T$ activator is administered by intravenous infusion in a dose to humans that is calculated according to the formula (I) single dose (mg/kg)=(0.01 to 20) * N (I) where N is the number of weeks between treatments such that N is between about 3 and about 4.

Claim 100 (New): The method according to claim 80, further comprising separately administering to a subject in need thereof an effective amount of a $\gamma\delta T$ activator and an interleukin-2 polypeptide.

Claim 101 (New): The method according to claim 100, wherein the interleukin-2 polypeptide is administered over a period of time comprised between 1 and 10 days.